REMARKS

Summary of Amendments

New claim 35 has been added. Support for claim 35 is found in claim 1 as filed and throughout the specification. No new matter has been added by this amendment.

Combined Declaration and Power of Attorney

The Examiner noted in Item 8 on page 2 of the Office Action that the oath and declaration filed on March 23, 2001 is defective. Applicants believe that this Supplemental Combined Declaration and Power of Attorney, taken with the Combined Declaration and Power of Attorney (filed as two counterparts on September 17, 1999), provide all required data under 37 C.F.R. § 1.63. Applicants believe no further documentation is needed.

Drawings

In response to Item 9 of the Office Action, Applicants note that formal drawings will be submitted upon receipt of a Notice of Allowance.

Claims

Applicants acknowledge with gratitude that the rejections under 35 U.S.C. 112, 2nd paragraph, have been withdrawn. Applicants also gratefully acknowledge that the rejection under 35 U.S.C. 103 over WO 94/18317 in view of US Patent 5,610,015 has been withdrawn.

Rejection Under 35 USC § 112, first paragraph

Claim 33 stands rejected for reciting "clavulanate" and "sulbactam" which, it is asserted, are not described in the specification. Applicants respectfully call the Examiner's attention to the specification on page 12, lines 3-5, which state "Both clavulanate and sulbactam are potent mechanism-based inactivators of β-lactamase." In addition, Applicants call the Examiner's attention to Table 2 on page 22. Table 2 lists "clavulanic" [acid] and "sulbactam" as drugs/irreversible inhibitors to the enzyme target "β-lactamase".

In view of these citations to "clavulanate" or "clavulanic" acid and to "sulbactam", Applicants respectfully submit that claim 33 has not introduced new matter and thus, fulfills the requirements of 35 U.S.C. 112, first paragraph.

Rejections Under 35 USC § 102 (b) and (e)

The Examiner has rejected claims 1, 6, 12, 17, 19, 20, and 23-24 under 35 USC § 102(b) as being anticipated by Licitra *et al* ("Licitra") and claims 1, 6, 12-17, 19, 20, 23, 24, 26, 27, and 31 under 35 USC § 102(e) as being anticipated by U.S. Patent No. 5,928,868 to Liu *et al* ("Liu"). Applicants traverse the rejections for the reasons described below.

Applicants and the Examiner appear to differ on whether Licitra or Liu anticipate the limitation that "ligand A forms an irreversible (covalent) bond with the predetermined target", as recited in claim 1. In the following paragraphs, Applicants set forth a meaning or sense for "irreversible" and for "covalent", and distinguish these terms from terms such as "reversible", "noncovalent" and "complex" without intending to limit, circumscribe or establish prosecution estoppel with regard to the invention recited in claim 1.

As generally used in chemistry and biochemistry, the word "irreversible", when used to describe the bonding between two moieties X and Y, intends that, under normal operating conditions the chemical bond between X and Y is not disrupted. By way of nonlimiting example, in biochemistry, a bond joining X and Y may be considered to be irreversible if the bond is not disrupted in an aqueous medium at temperatures, pH values, and other conditions at which living cells are viable.

Likewise, the word "covalent", as applied to a bond joining moieties X and Y intends that the bond involves the exchange of electrons in molecular orbitals that span the space between X and Y. The notion of a covalent bond is widely described and discussed in many texts and monographs that teach the subject matter of introductory chemistry, inorganic chemistry or organic chemistry. (For an exposition of molecular orbitals and their role in covalent bonds commonly encountered in organic chemistry, please see, by way of nonlimiting example, Kemp et al., "Organic Chemistry", Worth Publishers, Inc., New York, 1980, pages 19-30, which is included herewith as Exhibit A.)

As generally understood in chemistry and biochemistry, in images that depict or characterize the molecular structure of a compound, a solid line is conventionally employed to indicate a covalent bond joining two atoms. (For examples of the use of solid lines to indicate covalent bonds in organic chemistry as well as in inorganic chemistry, please see Kemp et al., pages 30-33 (Exhibit A)). This is pointedly seen in Licitra, for example, in Fig. 1, which shows the chemical structures for dexamethasone (upper left) and for FK506 (center left), and the synthetic reaction scheme leading to the formation of the dexamethasone-FKF06 hybrid ligand. In Fig. 1 every covalent bond between atoms is represented by a solid line (and organic chemical double bonds are represented by two parallel lines). It is emphasized to the Examiner that the presence of a line signifies a covalent bond and absence of a line signifies that no bond exists. (That this is conventional usage in chemistry is seen in Kemp et al., pages 32-33 (Exhibit A). In these pages, several examples are given showing the formation of new chemical bonds, which are indicated by the presence of a new solid line where the bond is formed.) Furthermore, the use of single-headed arrows in the reaction scheme of Fig. 1 signifies in a conventional way to the ordinary artisan that the reaction identified thereby may be considered to be irreversible. In such reactions the moieties newly joined to one another in the product of the reaction by the presence of a solid line between them, indicating the formation of a new covalent bond between their atoms.

In contrast, in the context of the present invention and the references cited in the Office Action, a complex between a ligand L and a receptor R in which L and R interact only by noncovalent bonds is not irreversible, but rather, is reversible. By this is meant that the L·R complex is susceptible of dissociation to produce L and R under normal operating conditions in biochemistry. As noted above, normal operating conditions include at least the conditions of an aqueous medium at temperatures, pH values and other conditions at which living cells are viable. Formation and dissociation of reversible, i.e. noncovalent, complexes is governed by the law of mass action:

$$L{\cdot}R \leftrightarrow L + R$$

and is characterized by a dissociation constant K_d given by the equation

$$K_d = [L][R] / [L \cdot R] .$$

The notion of a dissociation constant is frequently also discussed in terms of an affinity of binding, which is the inverse of the process of dissociation. The affinity may be evaluated quantitatively as the algebraic inverse of K_d.

Descriptions of reversible ligand-receptor interactions appear widely in textbooks of biochemistry. Three examples included with this reply are described here.

(1) Smith et al., "Principles of Biochemistry: General Aspects", Seventh Ed., McGraw-Hill Book Co., New York, 1983, discuss "Ligand-Receptor Interactions" on pages 290-292 (Exhibit B). Smith et al. describes the formation of "a complex RL" according to the Law of Mass Action, and provides the chemical equation describing the reversible formation and dissociation of the complex (page 291, bottom).

(2) Zubay, "Biochemistry", Addison-Wesley Publ. Co., Reading, MA, 1983 (Exhibit C), describes the mechanism of hormone action as being mediated by receptors. Hormone (H) binding to receptors (R) is presented in schematic fashion, using the arrows of chemical reactions, in Fig. 29-1 (page 1104) and especially in Fig. 29-2 (page 1105). Zubay states "[e]ach hormone binds with high affinity to biochemically distinct receptors." (page 1104) This statement emphasizes that the notion of "affinity" is employed in the description of reversible hormone- (or ligand-) receptor interactions.

(3) Voet et al., "Biochemistry" John Wiley & Sons, New York, 1990 (Exhibit D) describe reversible ligand-macromolecule binding in at least two contexts. On pages 212-213 Voet et al. discuss the reversible binding of the low molecular weight ligand O_2 to the proteins myoglobin and hemoglobin in terms of the arrows of reversible chemical reactions (for myoglobin on page 212, col. 2, top; and more generally for hemoglobin as a model for the binding of an enzyme E with its substrate S on page 213, col. 1, bottom). These chemical reactions are represented by equilibrium constants just below the respective chemical reaction equations on these pages. Voet et al. states "biochemists usually express equilibria in terms of dissociation constants, the reciprocals of the more chemically traditional association constants."

(page 212, col. 2, top). Voet et al. further characterizes receptor-ligand interactions in analogous fashion, providing a reversible chemical reaction scheme "according to the laws of mass action" (page 1153, col. 1, top) and the corresponding "dissociation constant", here called "K_L" (page 1153, col. 1, top).

The references presented in Exhibits A-D, and discussed above, clearly set forth the distinction between covalent binding, designated in chemical structural formulas by a solid line joining the bonded moieties, and the reversible binding involved in noncovalent complex formation. Furthermore, the references define the term "dissociation constant" and "affinity", as used in the prior art. Applicants employ the concepts presented in this section in their analysis of the prior art rejections below.

Liu 102 (e) rejection

The Office Action, referring to Fig. 2 of Liu, states "the reference teaches the binding of ligand 'A'[sic, Fig. 2 of Liu refers to a ligand hybrid constituted of moiety 7a and moiety 7b] to the target (or the receptor)" (page 6) . The "binding" described in Liu, in Fig. 2, is noncovalent binding. This may be seen in the following analysis of Figs. 2 and 3c of Liu Fig. 2 shows several components or moieties that are covalently bonded together; these are indicated by solid lines joining the moieties. These covalently linked moieties are:

a) the Lex A DNA-binding domain (hexagon) covalently bonded to (solid line) Protein X (irregular, involuted pentagonal shape) (i.e., the Protein Hybrid #1);

b) the ligand hybrid constituted of moiety 7a (triangle) covalently bonded to (solid line) moiety 7b (semicircle) connected by a linker; and

c) the Protein Expressed by cDNA Library (irregular rectangle with one edge a concave circular arc) covalently bonded to (in direct contact with) the Transcriptional Activator (full circle) (Protein Hybrid #2).

In contrast, in Fig. 3c, the product of the interaction of the Ligand Hybrid with its two receptors is depicted without any solid lines joining them as 1) the triangle of moiety 7a matched to the triangular involuted pentagonal shape of the High Affinity Receptor for Triangle Ligand,

and 2) the semicircle of moiety 7b matched to the concave circular arc of the Protein Expressed by cDNA Library. The absence in Fig. 3c of any solid lines joining components of the associations of item 1) and of item 2), in distinction to the presence of solid lines described for a)-c) above, unambiguously shows that Liu intends that the moieties in the complexes of items 1) and 2) are not covalently or irreversibly bound to each other.

That Liu intends noncovalent interactions when discussing the "binding" of a ligand to a receptor moiety of the High Affinity Receptor for Triangle Ligand or the Protein Expressed by cDNA Library is also clearly indicated at col. 8, lines 31-46. Liu discusses affinities and K_d values for complex formation involving several hormone ligand-receptor pair interactions. This paragraph explicitly and unambiguously communicates that reversible, noncovalent interactions are contemplated in the three-hybrid system described in the reference.

The Office Action itself exhibits confusion over whether or not Liu discloses reversible or covalent binding. On page 6, on the 6th and 7th lines, the Office Action states "The reference does not recite that the binding of ligand 'A'[sic, Fig. 2 of Liu refers to a ligand hybrid constituted of moiety 7a and moiety 7b] to the target is 'irreversible'". (Emphasis added) Yet on page 6, on the 13th through 16th lines, the Office Action states "Since the reference ligand 'A' binds to the receptor, and in the absence of teachings by the reference that the ligand 'A' is cleaved from the receptor (or target) for the activation of the reporter gene, the bond between the ligand 'A' and the receptor is a covalent bond." (Emphasis added) As provided in the instant claims including independent claim 1 which recites in part "ligand A forms an irreversible (covalent) bond", the present invention regards the terms "irreversible" and "covalent" as being essentially indistinguishable in their meanings. Yet the Office Action contradicts itself with respect to these two terms, stating that the reference does not recite irreversible binding (lines 6-7 of page 6) on the one hand, and that the bond is a covalent bond (lines 13-16 of page 6) on the other hand. In view of this confusion, Applicants emphatically declare that Liu cannot be applied as an anticipatory reference against claims 1, 6, 12-17, 19-20, 23-24, 26-27 and 31.

In addition, the statement in the Office Action on page 6, on the 13th through 16th lines,

> "Since the reference ligand 'A' binds to the receptor, and in the absence of teachings by the reference that the ligand 'A' is cleaved from the receptor (or target) for the activation of the reporter gene, the bond between the ligand 'A' and the receptor is a covalent bond." (Emphasis added)

is incorrect. As pointed out above, Liu discuss affinities and dissociation constants for the ligands and their receptors at col. 8, lines 31-46. This discussion relates to associations formed by the ligands and their receptors that are reversible and noncovalent. Therefore the quoted sentence in the Office Action is untrue and cannot stand. For this reason this assertion in the Office Action cannot be applied against the instant claims.

Furthermore, the statement in the Office Action on page 6, on the 13th through 16th lines,

> "Since the reference ligand 'A' binds to the receptor, and in the absence of teachings by the reference that the ligand 'A' is cleaved from the receptor (or target) for the activation of the reporter gene, the bond between the ligand 'A' and the receptor is a covalent bond." (Emphasis added)

is inappropriately conclusory and unsubstantiated. The Office Action arbitrarily concludes "the bond between the ligand 'A' and the receptor is a covalent bond". Applicants emphatically assert that such an unsubstantiated interpretation of the reference must be supported by positive specific evidence drawn from the reference. Tthe MPEP, in section 2112 requires that the burden of proof is on the Examiner to support the conclusion stated in the Office Action: "EXAMINER MUST PROVIDE RATIONALE OR EVIDENCE TENDING TO SHOW INHERENCY.... In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." (MPEP, 8th Edition, 2112). The Office Action, however, provides no such "basis in fact and/or technical reasoning". Applicants conclude, therefore that this statement is merely conclusory. As such, this statement cannot support the rejection of the claims under 35 U.S.C. 102(e).

For all the reasons summarized above, Applicants conclude that claims 1, 6, 12-17, 19-20, 23-24, 26-27 and 31 are novel over Liu. They respectfully request that this rejection be withdrawn at this time.

Licitra 102 (b) rejection

The Office Action, referring to Fig. 2 of Licitra, states "the reference teaches the binding of ligand 'A' to the target (or the receptor)" (page 5). Applicants submit that the "binding" described in Licitra, in Fig. 2, is noncovalent binding. This may be seen in the following analysis of Fig. 2 of Licitra, which shows several components or moieties that are covalently bonded together; these are indicated by solid lines joining the moieties. These covalently linked moieties are:

a) the DNA-binding domain (hexagon) covalently bonded to (solid line) the Receptor for Ligand A (irregular, involuted pentagonal shape) (i.e., the Hook);

b) the hybrid ligand constituted of ligand A (triangle) covalently bonded to (solid line) ligand B (semicircle) connected by a linker (see legend to Fig. 2; the Bait); and

c) the Receptor for Ligand B (irregular rectangle with one edge a concave circular arc) covalently bonded to (solid line) the Transactivation Domain (full circle) (the Fish).

In contrast, in the bottom half of Fig. 2, the product of "Fruitful Ligand-Protein Interactions" is depicted without any solid lines joining them as 1) the triangle of ligand A matched to the triangular involuted pentagonal shape of the Receptor for Ligand A, and 2) the semicircle of ligand B matched to the concave circular arc of the Receptor for Ligand B. The absence of any solid lines joining components of the associations of item 1) and of item 2, in distinction to the presence of solid lines described for a)-c) above, unambiguously shows that Licitra intends that the moieties in the complexes of items 1) and 2) are not covalently or irreversibly bound to each other.

That Licitra intends noncovalent interactions when discussing the "binding" of a ligand to a receptor moiety of the Hook or the Fish is also clearly indicated on page 12820, col. 2, second paragraph. Licitra discusses affinities and K_d values for complex formation involving several hormone ligand-receptor pair interactions. This paragraph explicitly and unambiguously communicates that only reversible, noncovalent interactions are contemplated in the three-hybrid system described in the reference.

The Office Action itself exhibits confusion over whether or not Licitra discloses reversible or covalent binding. On page 5, on the 3rd and 4th lines, the Office Action states "The reference does not recite that the binding of ligand 'A' to the target is 'irreversible'". (Emphasis added) Yet on page 5, on the 9th through 12th lines, the Office Action states "Since the reference ligand 'A' binds to the receptor, and in the absence of teachings by the reference that the ligand 'A' is cleaved from the receptor (or target) for the activation of the reporter gene, the bond between the ligand 'A' and the receptor is a covalent bond." (Emphasis added) As recited in the instant claims including independent claim 1 which recites in part "ligand A forms an irreversible (covalent) bond", the present invention regards the terms "irreversible" and "covalent" as being essentially indistinguishable in their meanings. Yet the Office Action contradicts itself with respect to these two terms, stating that the reference does not recite irreversible binding (lines 3-4 of page 5) on the one hand, and that the bond is a covalent bond (lines 9-12 of page 5) on the other hand. In view of this confusion, Applicants emphatically declare that Licitra cannot be applied as an anticipatory reference against claims 1,6, 12, 17, 19, 20, and 23-24. This indicates that claims 1,6, 12, 17, 19, 20, and 23-24 are novel over Licitra.

In addition, the statement in the Office Action on page 5, on the 9th through 12th lines,

> "Since the reference ligand 'A' binds to the receptor, and in the absence of teachings by the reference that the ligand 'A' is cleaved from the receptor (or target) for the activation of the reporter gene, the bond between the ligand 'A' and the receptor is a covalent bond." (Emphasis added)

is incorrect. As pointed out above, Licitra discuss affinities and dissociation constants for the ligands and their receptors on page 12820, col. 2, second paragraph. This clearly means that the associations formed by the ligands and their receptors are reversible and noncovalent. Therefore the quoted sentence in the Office Action is untrue and cannot stand. Therefore this assertion in the Office Action cannot be applied against the instant claims.

Furthermore, the statement in the Office Action on page 5, on the 9th through 12th lines,

> "Since the reference ligand 'A' binds to the receptor, and in the absence of teachings by the reference that the ligand 'A' is cleaved from the receptor (or target) for the activation of the reporter gene, the bond between the ligand 'A' and the receptor is a covalent bond." (Emphasis added)

is inappropriately conclusory and unsubstantiated. The Office Action arbitrarily concludes "the bond between the ligand 'A' and the receptor is a covalent bond". Applicants emphatically assert that such an unsubstantiated interpretation of the reference must be supported by positive specific evidence drawn from the reference. As provided in the Manual of Patent Examination and Practice, Rev. 1, August, 2001 (MPEP), the burden of proof is on the Examiner to support the conclusion stated in the Office Action.

> "EXAMINER MUST PROVIDE RATIONALE OR EVIDENCE TENDING TO SHOW INHERENCY The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993)(reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). >"To establish inherency, the extrinsic evidence `must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)(citations omitted)....
>
> In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)" (Emphasis added; MPEP, 7th Edition, 2112).

The Office Action, however, provides no such "basis in fact and/or technical reasoning". Applicants conclude, therefore that this statement is merely conclusory. As such, this statement cannot support the rejection of the claims under 35 U.S.C. 102(b).

For all the reasons presented above, Applicants conclude that claims 1,6, 12, 17, 19, 20, and 23-24 are novel over Licitra They respectfully request that this rejection be withdrawn at this time.

Rejection Under 35 USC § 103 (a)

The Examiner has rejected claims 1, 6, 12, 17, 19, 20, 23-24, 26-27, 31, 32 and 34 over Licitra.

"[I]n constructing a prima facie case of obviousness, when applying 35 U.S.C. 103, the following tenets of patent law must be adhered to:

(A) The claimed invention must be considered as a whole; [and]

(B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination..."[citing Hodosh v. Block Drug Co., Inc., 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986)].

"Finally, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings" (MPEP, 2141, 2143).

The present invention of claim 1, considered as a whole, relates to a method for identifying a cellular component to which a small molecule is capable of binding. The method includes the steps of:

(a) providing a hybrid ligand consisting essentially of two ligands, identified as ligand A and ligand B that are linked together, wherein

(i) ligand A has a specificity for a predetermined target;

(ii) ligand A forms an irreversible (covalent) bond with the predetermined target;

(iii) and ligand B is the small molecule;

(b) introducing the hybrid ligand into at least one sample, the sample containing an environment, the environment containing;

(i) a first expression vector, comprising DNA encoding the target for ligand A, linked to a coding sequence for a first transcriptional module for expression as a first hybrid protein;

(ii) a second expression vector comprising a random DNA fragment encoding a polypeptide linked to a second transcriptional module for expression as a second hybrid protein; and

(iii) a third vector comprising a reporter gene wherein the expression of the reporter gene is conditioned on the proximity of the first and second hybrid proteins;

(c) permitting the hybrid ligand to bind covalently the first hybrid protein through ligand A and the second hybrid protein through ligand B so as to activate the expression of the reporter gene;

(d) identifying those samples expressing the reporter gene; and

(e) characterizing the second hybrid protein in the samples identified in (d) so as to determine the cellular component to which the small molecule has a binding affinity.

Independent claim 31 considered as a whole, relates to a kit for detecting interactions between pharmacologically relevant small molecules and proteins that includes the following:

(a) a preactivated ligand A and reagents for forming a hybrid ligand with at least one type of ligand B, wherein ligand A has a specificity for a predetermined target and forms an irreversible (covalent) bond with the predetermined target;

(b) a first expression vector comprising DNA encoding a target for ligand A linked to a coding sequence for a first transcriptional module for expression as a first hybrid protein;

(c) a second expression vector comprising a random DNA fragment encoding a polypeptide linked to a coding sequence for a second transcriptional module for expression as a second hybrid protein;

(d) a third vector comprising a reporter gene wherein transcription of the reporter gene is conditioned on the proximity of the first and second hybrid proteins;

(e) an environment for transcription and translation of the first and second hybrid proteins and reporter genes; and

(f) a means for detecting the expression of the reporter gene following the formation of a trimeric complex between the hybrid ligand and the first and second hybrid proteins.

Licitra, considered as a whole, discloses a three-hybrid system. This system is adapted from the yeast two-hybrid system with which a third synthetic hybrid ligand is combined. Licitra disclosed the feasibility of this system by employing a hybrid ligand that is a heterodimer of covalently linked dexamethasone and FK506. The fusion proteins employed were a the hormone binding domain of the glucocorticoid receptor fused to the LexA DNA-binding domain, and of FKBP12 fused to a transcriptional activation domain (see Abstract). Licitra considered for all it discloses, fails to disclose forming an irreversible (covalent) bond between ligand A and a predetermined target. (Applicants stress that the covalent heterodimer of dexamethasone and FK506 of Licitra does not provide an irreversible (covalent) bond between ligand A and a predetermined target of the claimed invention.)

Furthermore, Licitra provides no suggestion or motivation to modify the reference to provide the instantly claimed invention. Licitra fails to suggest to or motivate the ordinary art worker to provide an irreversible (covalent) bond between ligand A and a predetermined target, as recited in claim 1. Licitra likewise fails to suggest to or motivate an ordinary art worker to provide a ligand A that has a specificity for a predetermined target and is preactivated to form an irreversible (covalent) bond with the predetermined target, as recited in claim 31. This indicates that Licitra fails to render the claimed inventions obvious.

The Office Action states "Thus the reference teaches the binding of ligand 'A' to the target (or receptor) and nowhere in the reference it teaches that the ligand "A' need to be activated before binding to the target...." (page 7, lines 11-13). Applicants note that the limitation "preactivated" appears only in the independent claim 31 drawn to a kit. Thus the quoted sentence relates only to claim 31, and not to claim 1 and the claims depending therefrom. Applicants agree with the quoted sentence, for it is true that Licitra does not disclose a preactivated ligand "A" that needs to be activated before binding to its target. Licitra fails to suggest to or motivate an ordinary artisan to provide a kit that includes a ligand "A" that needs to be activated before binding to its target. Thus claim 31, considered as a whole, is nonobvious over Licitra.

The Office Action further states, in the same sentence, "...nowhere in the reference it teaches that the ligand "A' need to be activated before binding to the target, that means that the ligand 'A' is preactivated." (page 7, lines 11-13). This juxtaposition of opposite statements is logically inconsistent, and confusing to Applicants. In view of this confusion, Applicants assert that this statement may not be employed as reasoning to support a case of obviousness of claim 31 over Licitra.

The Office Action additionally states "the reference does not recite that the binding of ligand 'A; to the target is 'irreversible'" (page 7, lines 15-16). Applicants agree with this statement. Licitra fails to motivate or suggest to an ordinary art worker to provide a method that includes employing a ligand A that forms an irreversible (covalent) bond with a predetermined target, as required by claim 1.

The Office Action again presents two confused statements in succession, the second diametrically opposed to the first. For immediately following the sentence quoted in the

preceding paragraph, an opposing sentence is presented: "the reference does not recite that the biding of ligand 'A; to the target is 'irreversible'. Thus, ligand 'A' binds to the receptor is irreversible." (page 7, lines 15-17). This juxtaposition of opposite statements is logically inconsistent, and confusing to Applicants. In view of this confusion, Applicants assert that this section of the Office Action may not be employed as reasoning to support a case of obviousness of claim 1 over Licitra.

Claims 32 and 34 are nonobvious over Licitra because the base claim, claim 1, is nonobvious over Licitra A claim that depends from a nonobvious claim is itself nonobvious.

Furthermore, the Office Action offers no evidence that knowledge generally available to one of ordinary skill in the art (MPEP § 2141) is available to render the instant claims obvious.

In summary, Applicants have shown that the Office Action fails to demonstrate that Licitra renders claims 1, 6, 12, 17, 19, 20, 23-24, 26-27, 31, 32 and 34 obvious. The Office Action is highly self-contradictory and does not sustain a case of obviousness. Applicants conclude that claims 1, 6, 12, 17, 19, 20, 23-24, 26-27, 31, 32 and 34 are nonobvious over Licitra They respectfully request that this rejection be withdrawn at this time.

CONCLUSION

Applicants submit that the Examiner's rejections have been overcome based on the enclosed amendments and remarks. Applicants therefore respectfully request that claims 1-6, 12-20, 23-24, 26-27 and 31-35 be found allowable at this time. Should any questions or issues arise concerning the application, the Examiner is encouraged to contact Applicants' undersigned attorney at the telephone number indicated below.

Respectfully submitted,

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VERSION MARKED TO SHOW CHANGES MADE

The Claims:

21. (Cancelled)

22. (Cancelled)

--35. (New) A method for identifying a cellular component to which a small molecule is capable of binding, comprising:

(a) providing a hybrid ligand consisting essentially of two ligands, identified as ligand A and ligand B that are linked together, wherein

(i) ligand A has a specificity for a predetermined target;

(ii) ligand A forms an irreversible (covalent) bond with the predetermined target;

(iii) and ligand B is the small molecule;

(b) introducing the hybrid ligand into at least one sample, the sample containing an environment, the environment containing;

(i) a first expression vector, comprising DNA encoding the target for ligand A, linked to a coding sequence for a first transcriptional module for expression as a first hybrid protein;

(ii) a second expression vector comprising a random DNA fragment encoding a polypeptide linked to a second transcriptional module for expression as a second hybrid protein; and

(iii) a third vector comprising a reporter gene wherein the expression of the reporter gene is conditioned on the proximity of the first and second hybrid proteins;

(c) permitting the hybrid ligand to bind covalently the first hybrid protein through ligand A and the second hybrid protein through ligand B so as to activate the expression of the reporter gene, thereby reducing a three-hybrid system to a two-hybrid system;

(d) identifying those samples expressing the reporter gene; and

(e) characterizing the second hybrid protein in the samples identified in (d) so as to determine the cellular component to which the small molecule has a binding affinity.--

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